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The Evolution of the Current Indications for Sentinel Lymph Node Biopsy in Breast Cancer

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Abstract

The aim of this literature review was to derive detailed information on the indications for sentinel lymph node biopsy (SLNB) in specific subgroups of patients with breast cancer, according to current evidence, in an era when the dogma of complete axillary lymph node dissection (ALND) is being challenged.

Key words: *Sentinel lymph node biopsy; breast cancer*

Introduction

Axillary nodal staging in primary breast cancer continues to be one of the most crucial prognostic factors in breast cancer treatment. Sentinel lymph node biopsy (SLNB) has been established as the gold standard in clinically node negative breast cancer, and has superseded axillary lymph node dissection (ALND). SLNB provides adequate information on which to make decisions (considered in any decision making concerning) concerning adjuvant therapies, with the same disease-free survival (DFS) and overall survival (OS) rates as ALND, without the complications of ALND, such as shoulder pain, impaired movement, numbness and lymphedema of the arm [1]. On the other hand, noninvasive methods for staging the axilla, such as clinical examination, ultrasonography (U/S), mammography, computed tomography (CT) and positron emission tomography (PET) are not considered sufficiently sensitive [2, 3]. SLNB has been extensively studied and found reliable, and it is currently the optimal method of axillary staging, with few side effects. However, controversies about the indications for SLNB in specific subgroups of patients and its timing are subjects of ongoing debate. This review focuses on the evolution of the current indications for SLNB in early breast cancer.

A search was made for English, Italian and Greek language literature/abstracts on SLNB in Pubmed, San Antonio Breast Cancer Symposium, clinicaltrials.gov database, and the guidelines of the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology (ESMO).

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Preoperative axilla evaluation

Preoperative clinical evaluation of axillary lymph nodes separates patients with breast cancer into two categories; patients with clinically positive nodes undergo ALND and patients with clinically negative nodes undergo SLNB. The SLNB approach is also acceptable in patients who have a clinically positive axilla not confirmed by preoperative biopsy, provided that SLNB is followed by simultaneous removal of all palpable nodes.

Axillary U/S staging combined with U/S guided biopsy is considered a feasible, effective method of preoperative axillary evaluation. Houssami and colleagues, in an updated meta-analysis of the clinical utility of axillary node U/S-needle biopsy concluded that the method has a positive predictive value (PPV) of 100%, a sensitivity of 50% and a false negative rate (FNR) of 25% [4]. A German prospective randomized clinical trial, the Intergroup-Sentinel-Mamma (INSEMA) trial, and the Sentinel node vs Observation after axillary UltrasounD (SOUND) trial of the European

Abbreviations

SLNB= Sentinel lymph node biopsy
ALND= Axillary lymph node dissection
DCIS= In situ ductal carcinoma
IR= Identification rate
FNR= False negative rate
ASCO= American Society of Clinical Oncology
NCCN= National Comprehensive Cancer Network
ESMO= European Society of Medical Oncology
pCR= Complete pathological response
DFS= Disease free survival
OS= Overall survival
IHC= Immunohistochemistry
AMAROS= After mapping of the axilla: radiotherapy or surgery
ACOZOG Z0011= American College of Surgeons Oncology Group Z0011
MBq= Megabecquerel (units of radiation dose)

Institute of Oncology investigated whether U/S staging of the axilla could substitute SLNB in cT1N0 patients [5,6]. Nomograms can accurately predict the cancer specific survival of T1 breast cancer patients, and also estimate the survival benefit of SLNB in these patients [7].

The definitive studies on axillary nodes were ACOSOG Z0011 "A randomized trial of axillary node dissection in women with clinical T1-2 N0M0 breast cancer who have a positive sentinel node" [8], and "Radiotherapy or surgery after a positive sentinel node in breast cancer (AMAROS) [9]. In the post Z0011 and AMAROS era, with well-defined criteria, not all patients with positive SLNB require ALND. According to ASCO 2014 and NCCN guidelines 2018, when all Z0011 criteria are met, ALND can be omitted safely without any survival compromise, with clinically negative nodes, T1/2, fewer than 3 metastatic SLNs, breast-conserving surgery and whole breast irradiation [8,9]. The type of systemic therapy is increasingly being determined by tumor biology and not the predictive value of the axillary status. Consequently, Z0011 ineligible patients should be identified preoperatively so that preoperative assessment with axillary U/S can be omitted. [8,10,11] In a recent study, patients with positive axillary nodes on U/S guided biopsy carried a higher positive burden in the case where more than 3 nodes were positive [12]. This subgroup of patients should be considered Z0011 ineligible and proceed to upfront ALND without SLNB [10,12-14]. Women with SLN metastases who will undergo mastectomy are also Z0011 ineligible and should be offered ALND. The efficacy, safety and feasibility of the method varies between centers and further guidelines should be defined to benefit U/S node positive patients [15,16].

Evolution of the SLNB technique

The SLNB approach was first introduced by Cabanas [17] for staging penile cancer, and evolved by Morton for patients with melanoma [18]. Metastatic cancer cells follow lymph vessels and settle in the first SLN. Following injection of a tracer, all blue-dyed or radioactive nodes are removed, usually up to 4-5 nodes, along with removal of any enlarged nodes encountered, possibly due to blocked lymphatic channels. A combination of radioactive tracer (40-60 MBq) and blue dye (0,5-5 ml) is commonly injected subdermally, subcutaneously or peritumorally. Superficial injection distributes the tracer more rapidly while deeper injection detects more SLNs. A short incision at the lower hairline of the axilla or at the area with the highest probe signaling is preferred, and up to 4-5 SLNs are removed. Nodes with more than 10% radioactivity of the first SLNs, and any other enlarged, suspicious nodes are removed.

Other recently used tracers are superparamagnetic iron oxide (SPIO, Sienna+) and indocyanine green (ICG), and single emission computed tomography camera SPECT/CT may be used.

Fluorescent optical intraoperative image-guided SLNB using ICG has become more widely used and may be a useful alternative to radiocolloid because it is widely available at low cost, results in a high SLN identification rate and low FNR, especially when combined with a blue dye. Furthermore, it avoids the need for considerable surgical experience and reduces the occurrence of allergic reactions [19]. The method was endorsed by ESMO guidelines 2015.

SPIO is injected subcutaneously and detected by a handheld magnetometer, and by visualization of the black or brown staining of the lymph nodes. The main drawbacks of the method are that it is time consuming and the residual magnetic tracer in the injection site can remain for a long period and in some patients may cause artefacts on postoperative MRI [20].

Indications for SLNB in early breast cancer

SLNB is indicated in patients with early breast cancer (T1 orT2 <5cm), which is clinically node negative (cN0), and in patients with ductal carcinoma in situ (DCIS) who undergo planned mastectomy [11,21]. The accuracy of SLNB depends on a brief learning curve and the anatomical drainage differentiation of the breast. When the operation is performed by surgeons familiar with the technique, detection rates are 97-98%. The FNR for SLNB is to 5-9.8%% (Table 1). In 2005, ASCO confirmed a lower FNR using the dual mapping compared with single method (7% versus 9.9%). Negative SLNB negates the need for ALND, which offers no further prognostic information or clinical benefit. It is less invasive and engenders less complications [22].

Table 1. *Clinical trials evaluating the accuracy of Sentinal Lymph Node Biopsy (SLNB).*

	Identification Rate (IR)	False negative rate (FNR)
NSABP B32 trial [23]	97.2%	9.8%
MILAN trial [22]	99%	8.8%
SNAC trial [24]	94%	5.5%
GIVOM trial[25]	95%	16.7%
ALMANAC trial [26]	96%	6.7%

NSABP: National Surgical Adjuvant Breast and Bowel Project
MILAN: Sentinel-lymph-node biopsy as a staging procedure in breast cancer
GIVOM: Sentinella-GIVOM Italian randomised clinical trial
SNAC: NHMRC Sentinel-lymph-node-based management or routine axillary clearance?
AMANAC: Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer

SLNB in locally advanced breast cancer

ALND is indicated instead of SLNB in patients with clinically positive axillary lymph nodes and locally advanced T4 or inflammatory breast cancer T4d, on account of the high FNR due to obstructed lymphatic drainage. Many centers consider SLNB acceptable in cT3N0 patients, but recent ASCO guidelines recommend against SLNB in this subgroup of patients [21].

SLNB in older age patients

Older age is not considered a contraindication for SLNB, but SLNB can be omitted in older women whose axillary status does not affect the decision for adjuvant treatment in a multidisciplinary setting. Sparing SLNB in early, small, favorable breast cancers is under investigation [5,6]. Application of a nomogram predicting axillary lymph node status can reduce operation time and cost, and lower the reoperation rate by up to 1.6% [7,27].

SLNB in ductal carcinoma in situ (DCIS)

SLNB is not indicated in breast conserving DCIS. By definition, DCIS cannot metastasize and less than 1% of patients with DCIS will develop invasive breast cancer yearly [28]. Axillary metastasis was 3/620 after 15 years in the NSABP-B17 trial, and 6/1,799 after 12 years in the NSABP-B24 trial [29]. According to the "rule of 20", DCIS constitutes 20% of newly diagnosed breast cancers, 20% of DCIS diagnosed by core biopsy upgrade to invasive cancer after surgery, and 20% of DCIS treated by mastectomy have axillary metastasis [28-30]. Consequently, SLNB is indicated after planned mastectomy for DCIS or extensive DCIS (>5cm) clinically suspected of having coexisting invasive disease (10-20%) [30]. SLNB can be omitted with breast conserving DCIS, and performed if necessary after the final pathology report, as a second operation.

SLNB after previous breast/axillary surgery

With advances in the therapeutic management of breast cancer, patients achieve long survival rates, and approximately 5% to 10% will develop local recurrence in the breast or chest wall. The standard treatment in these patients was re-excision or salvage mastectomy with ALND. In most of these patients with cN0 axilla, positive nodes were found only in few and most of them had been subjected to ALND unnecessarily.

SLNB is still feasible after previous breast surgery where the drainage pattern is distorted. It is recommended even after previous SLNB or ALND, with a lower detection rate of around 60-70% [21,31-33]. Preoperative lymphoscintigraphy can elucidate the drainage pattern in these cases. In a meta-analysis of 1,000 patients, an aberrant lymphatic drainage pattern was detected in 26% [34]. In 3-4% of cases a SLN is detected in the opposite axilla [31]. In a recent French study, previous breast surgery did not affect the accuracy of SLN biopsy. A sufficient interval, of greater than 36 days, is recommended between the two operations, which can improve the SLN detect rate by up to 85.5% [35]. Because of a higher rate of SLNB identification failure, ALND is recommended when SLNs cannot be retrieved [33].

SLNB in multicenter/multifocal breast cancer

The SLNB method is also recommended for multifocal/multicentric breast tumors [21]. It is a safe and feasible method, as all breast quandrants drain to the same lymph nodes [36]. In a multicenter study of 1,214 women in whom multifocal and multicentric tumors were 9,3% and 2,6% respectively, the detection rate of SLNB did not differ [37].

SLNB in pregnancy

The ASCO 2016 guidelines recommend against SLNB in pregnancy [21]. Recent studies, however, suggest that SLNB using radioisotope only is accurate and safe in pregnancy due to its very low absorption by the fetus. Conversely, blue dye injection (isosulfane or methylene blue) carries a low (1%), but harmful, risk of anaphylactic reaction and possible teratogenic effects [38].

SLNB in male breast cancer

SLNB has not been well validated in male patients with breast cancer. The documented studies are retrospective and include a small number of patients, usually treated by mastectomy and ALND [39].

Timing of SLNB: before or after NACT in patients with clinically negative axilla (cN0)

The indications for primary systemic therapy include tumor and axilla downstaging and eligibility for breast conserving surgery. The complete pathological response (pCR) to neoadjuvant chemotherapy (NACT) is an excellent surrogate for disease free survival (DFS), although a significant survival benefit has not yet been demonstrated [40].

In the neoadjuvant setting, the choice of performing SLNB before or after NACT in patients with locally ad-

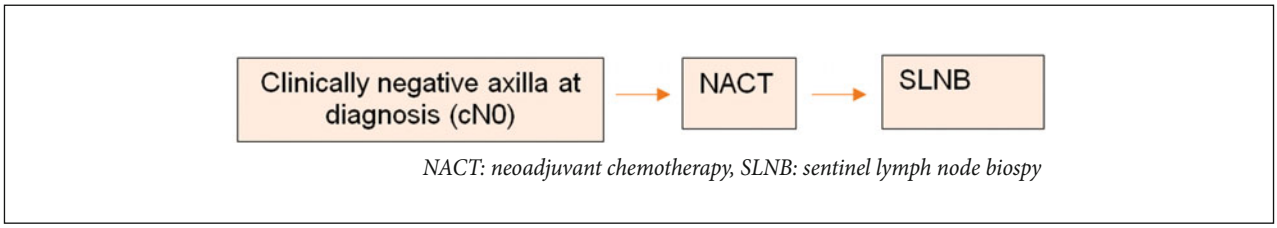

Figure 1. Procedure in patients with breast cancer with clinically negative axilla at diagnosis.

vanced breast cancer is still a subject of debate. SLNB may be recommended before NACT in cases of clinically negative axilla (cN0), with the same FNR as patients not planned for NACT. Staging of the axilla upfront by U/S and fine needle aspiration (FNA), however, cannot replace SLNB, as it is associated with a sensitivity of only 21–25% in finding axillary metastasis in cN0 [41] (Figure 1).

In the four-part German SENTINA study of 1,737 patients, the detection rate was 99.1% before NACT [42]. The French prospective multicenter ganglion Sentinelle et Chimiotherapie Neoadjuvante GANEA study enrolled 195 cN0 patients with a 90% identification rate and 11.5% FNR, and confirmed the feasibility of SLNB after NACT [43].

Van der Heiden-van der Loo and colleagues conducted a population based study including 980 patients undergoing SLNB before NACT and 203 patients undergoing SLNB after NACT. The SLN identification rate was higher in the SLNB before NACT group than in the SLNB after group (98% versus 95%), but significantly less patients assessed before NACT had a negative SLN than those assessed after (54% versus 67%) and, consequently, the additional axillary treatment (ALND and radiotherapy) rate was significantly higher in the SLNB before NACT group (45% versus 33%) [44].

In a MD Anderson Cancer Center (MDACC) retrospective study, SLN identification rate, FNR and regional recurrence rate were compared between groups of 575 patients undergoing SLNB after NACT and 3,171 patients undergoing SLNB before NACT. The SLN identification rates between the two groups showed small differences (before 98.7% vs. after 97.4%). The FNR was similar between the two groups (before 4.1% vs. after 5.9%). At a median follow-up of 47 months, no differences were observed in DFS or OS between the two groups in locoregional recurrence (before 2.1% vs. after 3.3%) [45]. The ongoing GANEA 2 study of 590 patients who underwent SLND after NACT issued an interim report of a 97.3% identification rate, 12% FNR and 94.8% DFS. New results are expected; the study will be completed in July 2019 [46] (Table 2).

The advantage in performing SLNB upfront is that the identification rate is excellent and the nodal staging is unaffected by NACT. Accurate nodal staging may help in deciding on optimal chemotherapy before NACT, and the most adequate locoregional treatment after NACT, but two surgical interventions are required. SLNB after NACT has the advantage of only one operation and more patients can be spared an ALND, due to nodal downstaging in 20–40% [47]. Axillary staging after NACT has been reported to be better predictive of locoregional recurrence than axillary staging upfront, and therefore can be used to guide adjuvant locoregional treatment [48]. The disadvantages, however, are lower identification rates after NACT, a higher FNR and uncertainty on pre-treatment nodal stage. Nevertheless,

Table 2. *Studies on sentinal lymph node biopsy (SLNB) before or after neoadjuvant chemotherapy (NACT) in patients with breast cancer with clinically negative axillary nodes.*

	Patients					
	SLNB before NACT	SLNB after NACT	IR before NACT	IR after NACT	FNR before	FNR after
SENTINA [2013] [42]	1,022	-	99.1%			
GANEA [2009] [43]	-	195	-	90%		11.5%
VAN DER HEIDEN [2015] [44]	980	203	98%	95%		
MD ANDERSON CC [45]	3,171	575	98.7%	97.4%	4.1%	5.9%
GANEA 2 [2017] [46]	-	590	-	97.3%	-	12%

IR: Identification rate; FNR: False negative rate
SENTINA: Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy
GANEA: Sentinel lymph node biopsy after neoadjuvant chemotherapy for advanced breast cancer: results of Ganglion Sentinelle et Chimiotherapie Neoadjuvante

harvesting 3-4 SLN after dual mapping makes decisions on axillary surgery and adjuvant radiotherapy simpler, avoiding any risk of undertreatment. According to both the updated 2014 ASCO guidelines and the NCCN 2016 guidelines, women with cN0 operable breast cancer may be offered SLNB either before or after NACT in the absence of evident axillary nodal disease. In order to increase the sensitivity and accuracy of the procedure, at least 3 SLNs should be retrieved and complete ALND is advised, even if only one SLN is found to be positive [49,50]. Currently SLNB is eventually performed by most surgeons after NACT for patients with pretreatment cN0, de-escalating axillary surgery [51]. SLNB after NACT is recommended, provided that clinical examination and axillary U/S show no nodal progression.

SLNB in patients with clinically positive axilla (cN+) which becomes negative (ycN0) after NACT

Patients with clinically positive axilla (cN+) are re-evaluated after NACT and separated into those who become clinically negative and those who remain clinically positive. SLND may be performed in patients with cN+ before NACT that became cN0 afterwards (ycN0). Downstaging occurs in 40% of cN+ patients and when they are human epidermal growth factor receptor-2 (Her-2) positive the rate of complete pathological response (pCR) rises to 74% [52] (Figure 2).

Post-NACT axillary U/S (AUS) has been reported to be valuable in axilla restaging after NACT in patients with pretreatment positive axillary nodes. In the Z1071 trial, patients were grouped into AUS-suspicious patients and AUS-normal patients before surgery. AUS-suspicious patients had a significantly higher number of positive nodes and greater metastasis size compared with AUS-normal patients. In addition, the FNR of SLNB was reduced from 12.6% in the general patient population to 9.8% in the AUS-normal patients. This result suggests that post-NACT AUS allows selection of the patients with highest probability of axilla pCR and may offer them the opportunity of ALND omission in the case of negative SLNs [53].

The American Alliance study, ACOSOG Z1071, determined a pCR of 41%, an identification (IR) of 84.8% and a FNR of 10.7% in patients with SLNB after NACT using a dual agent and with more than 2 lymph nodes excised. The FNR was 8.7% when the immunohistochemical (IHC) staining was used and decreased to 6.8% when a lymph node clip was placed preoperatively [54,55] (Table 3). In the SENTINA prospective multicenter study, 592 patients ycN0 after NACT had an IR of 80% and overall FNR of 14.2%. When only one SLN was excised, the FNR increased to 24.3% but when more than 3 SLN were harvested and dual tracer used then the FNR dropped to less than 7% [42]. In the recent SN-FNAC prospective multicenter study, the IR was 87.6% and an overall FNR of 8.4% was achieved by the mandatory use of IHC. SLN metastases of any size, including isolated tumor cells (ypN0[i+], ≤ 0.2 mm), were considered

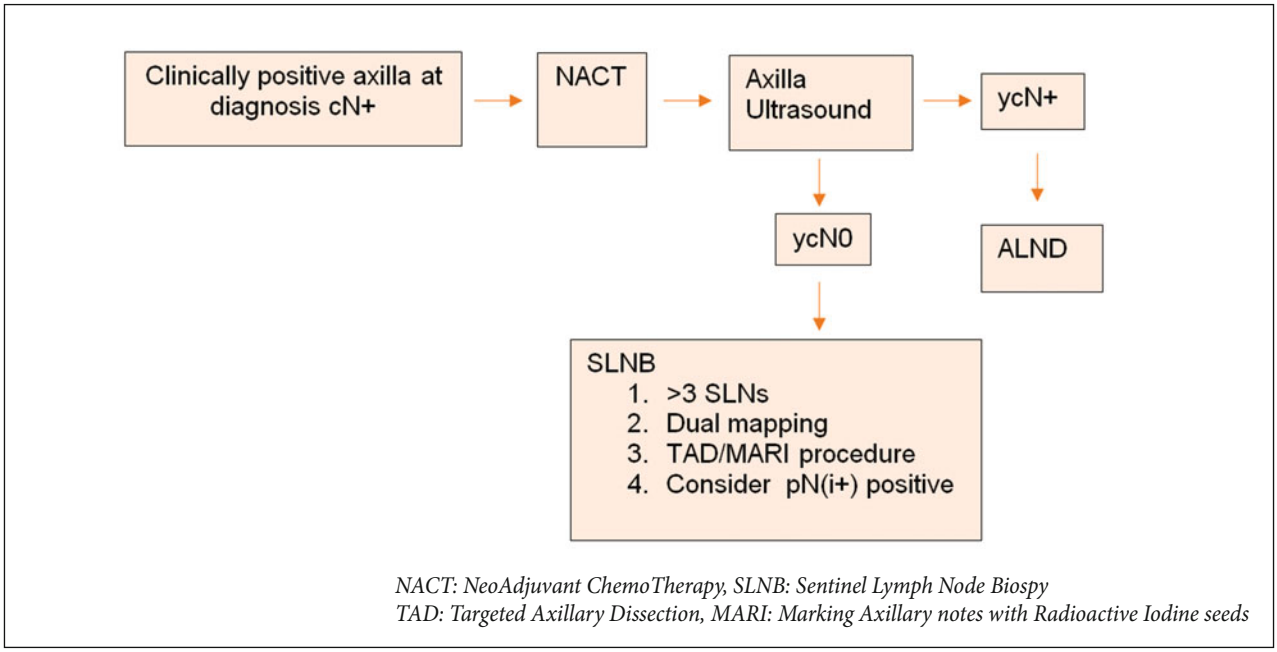

Figure 2. Procedure in Patients with breast cancer with clinically positive axilla at diagnosis

Table 3. *Studies on sentinal lymph node biopsy (SLNB) after neoadjuvant chemotherapy (NACT) in patients with breast cancer with clinically or biopsy proven positive axillary nodes.*

	Studies						
	ACOSOG Z1071 (2016) [53]	SENTINA (2013) [42]	SN FNAC (2013) [56]	Classe review 2016) [46]	El Hage Chehade (2016) [60]	TAD procedure (Boughey 2016) [55]	MARI procedure (Donker 2015) [61]
Patients (N)	756	592	153	1,395	2,471	208	100
FNR overall	12.6%	14.2%	13.3%	15.1%	16%	10%	-
FNR (IHC)	8.7%	-	8.4%	-	8.7%	-	-
Single agent mapping	20.3%	16%	16%	-	-	10%	-
Dual agent mapping	10.8%	8.6%	5.2%			10.3%	
FNR 1 SLN	-	24.3%	1.,2%	23.9%	-	7.7%	
>2 SLNs	21.1%	18.5%	4.9%	10.4%			
>3 SLNs	9.1%	4.9%					
marking						1,4%	7%

FNR: false negative rate;
SLN: sentinel lymph node
IHC: immunohostochemistry used FNA

positive. When more than 2 SLNs were excised, the FNR decreased to 4.9% and accuracy increased to 96.8%. Dual tracers were associated with FNR of 5.2% [56]. A recent Italian study with 5-year follow-up suggested that SLNB after NACT is acceptable and safe, especially in patients who have pCR to NACT and become ycN0 [57]. A prospective study conducted by the Sloan Kettering Memorial Cancer Center in the USA enrolled 288 cN+ patients in the years 2013–2015. Nearly 70% were eligible for SLNB after NACT, and for 48% axillary dissection was avoided, supporting the role of NACT in reducing the need for ALND among patients presenting with nodal metastases [58]. In a Swedish prospective multicenter study recruiting 224 patients, the IR was 69.4% (at least one SLN), and 77% of patients with a positive SLNB before NACT had no positive axillary lymph nodes after NACT. Conversely, 7.4% of patients had a negative SLNB before NACT but became positive after (FNR 7.4%) [59]. In another recently published systematic review and meta-analysis involving 3,398 patients with positive ALNs prior to NACT from 19 studies, the pooled estimate of SLN identification rate and FNR of SLNB after NACT were similar, being 90.9% and 13% respectively [60].

Various methods have been suggested to lower FNR of SLNB after NACT. Pre-NACT clipping or radioactive seed marking of the biopsy-proven nodes is currently under investigation. The MARI procedure, i.e., marking the axillary lymph node with radioactive iodine seeds, is a new minimal invasive method [61]. Targeted axillary dissection (TAD) by clipping biopsy-proven involved SLNs before NACT was evaluated in a study from the MD Anderson Cancer Center. The clipped node was located using iodine-125 seed localization; the FNR was determined in patients undergoing complete axillary lymph node dissection. The FNR of the clipped node was only 4.2%. In 23% of patients, the clipped node was not the sentinel [62]. Trials such as GANEA 3, the Alliance A011202 and Swedish SENOMAC, which are ongoing, are expected to further elucidate the comparative feasibility and efficacy of SLNB/ALND in the neoadjuvant setting.

Taking all the current evidence into consideration, SLNB may be considered in patients with cN+ axilla that become clinically and radiologically negative after NACT. Optimization of SLNB after NACT could be achieved by the use of dual tracer lymphatic mapping, identification and retrieval of >2 SLNs, with the use of IHC for disease detection in SLNs and planned completion ALND in patients with pN(i+) disease.

In conclusion, the role of surgery in axillary staging and the planning of breast cancer treatment is changing. Nowadays, high-morbidity radical resections are being abandoned. Continuous improvement in cure rates and better quality of life without compromising the oncological outcome is the main aim of modern breast cancer surgery. Today's breast surgeons should be well informed of the current evidence concerning the cardinal role of SLNs, and become familiar with all the emerging modalities concerning the comprehensive treatment of breast cancer, with the potential to de-escalate axillary surgery.

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